Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-45 are pending in the application, with 1 being the independent claim. Support for the amendment to claim 1 and new claims 29-45 can be found throughout the specification, specifically, at paragraphs [0082] and [0086], and in the claims as originally filed. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 102

A Claims 1, 2, 5, 8-10 and 15-22 (Method)

The Examiner has rejected claims 1, 2, 5, 8-10 and 15-22 under 35 U.S.C. § 102(b) as allegedly being anticipated by Evans *et al.* (International Publication No. WO 02/00844, Published PCT Appl. No. PCT/US01/20200, hereinafter "Evans"). The Examiner asserts that:

> Evans teach a method of preparing a lyophilized composition comprising: (a) mixing (i) a polyoxyethylene (POE) and a polyoxypropylene (POP) block copolymer such as CRL-1005; (ii) a polynucleotide; (iii) an instantly recited cationic surfactant; (iv) an glycerol amorphous cryoprotectant; and a physiological buffer at a temperature below the cloud point of said block copolymer to form a mixture having the recited concentrations and (b) lyophilizing the mixture. (OA at page 5.)

Specifically, the Examiner asserts that "Evans teach the inclusion of glycerol, an amorphous cryoprotectant, as defined by the specification at paragraph [0079]." (OA at page 4.) Additionally, the Examiner further alleges that the incorporated reference WO97/40839 "teach the lyophilization of DNA vaccines in the presence of appropriate formulation excipients." (OA at page 4.) Applicants respectfully traverse this rejection.

To anticipate a claim, the reference must teach *every* element of the claim. *See* MPEP § 2131 (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989).

Evans does not recite a method of preparing a lyophilized composition comprising a cryoprotectant selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and mixtures thereof, or a crystalline bulking agent. Evans teaches that the combination of DNA and CRL-1005 results in particles (aggregates), and that these particles can be used as an immunogen. The association of DNA to the copolymer particle leads to an increased immune response in an animal. (page 10, lines 26-29.) The reference teaches that the concentration of benzalkonium chloride (BAK) has a significant effect on the particle size, as well as DNA binding to the copolymer. (Figure 6.). "It is the formation of this copolymer/surfactant adjuvant particle during warming which promotes enhanced association of polynucleotide molecules to the particle and in turn which enhances the adjuvant properties of this microparticle." (page 15, lines 14-17.) Evans only teaches

freezing the CRL-1005, DNA, BAK composition to -70°C and does not teach lyophilizing the mixture.

Evans teaches using a cationic surfactant, BAK, to promote the association of the polynucleotide with the copolymer, CRL-1005, during freeze-thaw cycles. (page 38, lines 18-23.) The reference does not teach lyophilizing the mixture, or using glycerol to prevent aggregate formation with a lyophilized polynucleotide / copolymer mix. Evans teaches that the additive glycerol is thought to be a non-reducing free radical scavenger. (page 30,lines 30-34.) The incorporated reference, WO 97/40839, teaches that the formation of free radicals during the freeze-drying procedure is detrimental to the DNA. (see WO 97/40839, claim 11.) The incorporated reference teaches that the addition of glycerol as a free radical scavenger during lyophilization. Thus, the rationale for using glycerol in Evans is to prevent the formation of free radicals with the DNA and not to use glycerol as an amorphous cryoprotectant during lyophilization.

Evans does not disclose lyophilization of any composition. Even though the incorporated reference WO97/40839 teaches lyophilizing a polynucleotide mixture, the incorporated reference does not teach using an amorphous cryoprotectant in conjunction with a block copolymer as presently claimed in the procedure. Because neither Evans nor the incorporated reference disclose each and *every* element of the claimed invention, Evans cannot anticipate the invention. Applicants respectfully request that the rejection be reconsidered and withdrawn.

B. Claims 23, 24, 27 and 28 (Product)

The Examiner has rejected claims 23, 24, 27 and 28 under 35 U.S.C. § 102(b) as allegedly being anticipated by Evans. Specifically, the Examiner asserts that Evans "clearly teaches a composition comprising POE and POP block copolymer; a polynucleotide; a cationic surfactant; and a glycerol amorphous cryoprotectant or a crystalline bulking agent." (OA at page 5.) Applicants respectfully traverse this rejection. The shortcomings of Evans as it applies to the presently amended claims have been discussed above.

The invention of claims 23, 24, 27 and 28 relates to the production of a freeze dried polynucleotide / copolymer mixture. The copolymer is an adjuvant that stimulates the immune response. The problem with lyophilizing microparticles, especially particles comprising copolymers, is that they tend to aggregate during the lyophilization process. Once aggregates are formed, these aggregates will not redisburse into microparticles when reconstituted. The formation of aggregates or fusion products leads to a population of varying sized particles. (specification paragraph [0005].) The addition of the cryoprotectant allows the product to be reconstituted so that the product will maintain its optimal particle size. (specification paragraph [0003].) The presently claimed invention prevents the formation of aggregates or fusion products during the lyophilization procedure. (specification paragraph [0003].) Thus, the particle size and polydispersity of the microparticles remain substantially unchanged upon reconstituting the lyophilized powder. (paragraph [0066] and table 1.)

To anticipate a claim, the reference must teach *every* element of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

Evans teaches the combination of the cationic surfactant, BAK, mixed with the DNA and CRL-1005. The inclusion of BAK is important to achieve the most efficient DNA copolymer association. Evans does not recite a composition comprising a cryoprotectant selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and mixtures thereof, or a crystalline bulking agent. Because Evans does not teach each and *every* element of the claimed invention Evans cannot anticipate the instant claims.

The claims require that the product is stable and mono-dispersed after reconstitution with an aqueous solution. Evans does not teach lyophilizing the polynucleotide so that it is stable and can be redisbursed with the addition of an aqueous solution. Even if the product taught in the examples in Evans were to be lyophilized the product would not result in a mono-dispersed composition after the addition of an aqueous solution. The composition in Evans would result in aggregate formation after lyophilization and reconstitution, thereby, the composition is structurally different from the presently claimed composition. Table 1 in the specification compares (paragraphs [0125] and [0126]) a polynucleotide complex lyophilized in a solution consisting of PBS, CRL-1005 and BAK, as taught by the examples in Evans, with a polynucleotide that is lyophilized in 10 mM phosphate buffer, 10% sucrose solution, BAK and CRL-1005. In the absence of an amorphous cryoprotectant during lyophilization with the CRL-1005 composition, the resultant product aggregated into larger particles, thus, the reconstituted particles are not mono-dispersed. Because Evans does not teach a stable mono-dispersed product after the addition of an aqueous solution, Evans does not teach

each and *every* element of the claimed invention and, therefore, cannot anticipate the claims.

Evans does not disclose lyophilization of any composition. The incorporated reference does not remedy the shortcomings of Evans. The incorporated reference, WO 97/40839, teaches lyophilization of DNA, in the presence of sucrose, sodium chloride and potassium phosphate. (WO 97/40839, see claims.) The reference does not teach or suggest using a copolymer in the lyophilization mixture. Because neither Evans nor the incorporated reference disclose each and *every* element of the claimed invention, Evans cannot anticipate the invention. Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103

C. Claim 3 (Method)

The Examiner has rejected claim 3 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Evans in view of Balasubramanian (U.S. Pat. No. 5,824,322; hereinafter "the '322 patent"). The Examiner asserts that Evans teach a triblock and reverse triblock copolymer, however, "Evans does not teach a POP-POE-POP copolymer wherein POP accounted for up to 20,00 daltons of the mass of the copolymer and POE represents between 1% and 50% of the polymer by weight." (OA at page 6.) The Examiner further asserts that the '322 patent "teach compositions containing biologically-active copolymer comprising a reverse triblock copolymer of polyoxyethylene/polyoxypropylene" (OA at page 6); that the POP is between approximately 2,000 - 10,000 daltons; and that the POE is between approximately 2%

and 30%. (OA at page 7.) The Examiner additionally asserts "that such formulation may be presented and stored in freeze-dried (lyophilized) conditions only requiring the addition of sterile water prior to use." (OA at page 7.) Applicants respectfully traverse this rejection.

The Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the cited art. *See In re Piasecki*, 745 F.2d 1468, 1471-72 (Fed. Cir. 1984). A *prima facie* case of obviousness cannot be established unless all of the claim elements are taught or suggested by the cited references. *See In re Royka*, 490 F.2d 981, 984-85 (CCPA 1974); *see also In re Glaug*, 283 F.3d 1335, 1341-42 (Fed. Cir. 2002); *In re Rijckaert*, 9 F.3d 1531, 1533 (Fed. Cir. 1993). "[I]t is insufficient to merely identify each element in the prior art to establish unpatentability of the combined subject matter as a whole." *See Sanofi-Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1379 (Fed. Cir. 2006) *citing Abbot Labs. v. Andrex Pharm., Inc.*, 452 F.3d 1331, 1336 (Fed. Cir. 2006) In addition, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine reference teachings. *See In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Additionally, there has to be a reasonable expectation of success when combining the prior art references. *See In re Merck & Co., Inc.*, 800 F.2d 1091 (Fed. Cir. 1986) Also, the modification or combination can not change the principle of operation of the prior art. *See In re Ratti*, 270 F.2d 810 (CCPA 1959) In the present case, the Examiner's burden has not been satisfied.

i. There is no expectation of success in combining Evans and the '322 patent

One of ordinary skill in the art would not have been motivated to combine the disclosures of Evans and the '322 patent to arrive at the presently claimed invention because the combination does not teach all the claimed elements, and there would be no expectation of success. Evans teaches a formulation that include DNA: adjuvant particles suspended in cold solution. Evans teaches combining BAK, DNA and CRL-1005, and freezing the mixture. (page 32, lines 29-30.) Evans teaches that BAK affects the association of DNA with CRL-1005, increasing concentration of BAK increases DNA association with the copolymer. (page 36, example 3.) Evans does not recite a composition (a product) comprising a cryoprotectant selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers and proteins, or a crystalline bulking agent. Evans does not teach lyophilizing any composition. Thus, Evans does not teach each and every element of the present invention, because the reference does not teach using the amorphous cryoprotectant or a crystalline bulking agent as required by the amended claims. Additionally, the reference also does not teach or suggest using a reverse block copolymer having a molecular weight of POP up to approximately 20,000 daltons and a POE portion of approximately 1-50% by weight. Since Evans does not set forth a product comprising all the elements as recited in the presently pending claims, the reference cannot teach a method of making or preparing such a lyophilized composition. The shortcoming of Evans are not rectified in combination with the '322 patent, because the '322 patent does not teach a composition that comprises a POE/POP reverse triblock copolymer, a polynucleotide, a cationic

surfactant and an amorphous cryoprotectant or crystalline bulking agent. Further, the '322 patent does not disclose using a polynucleotide in conjunction with the block copolymer. The ordinary artisan would not have a reasonable expectation of success in arriving at the claimed invention by combining Evans with the '322 patent.

ii. Evans and the '322 patent do not relate to the same process

Evans teaches combining BAK, DNA and CRL-1005, and freezing the mixture. (page 32, lines29-30.) Evans teaches that BAK stabilizes a smaller particle size of the co-polymer, CRL-1005, and that the particle size is not significantly effected by warming through the cloud point. (page 34, lines 25-26.) Evans does not teach lyophilizing any composition. Freezing a composition is a different procedure than lyophilizing a composition. The process of lyophilizing a composition removes water from the composition, this forces the remaining molecules to come closer together, thereby, increasing the interactions between the molecules resulting in aggregate formation (specification paragraph [0005]). The freezing process results in the water molecules forming a solid structure, but does not remove the water from the composition. Even if the '322 patent, mentions lyophilizing a composition, the '322 patent does not teach a composition that comprises a POE/POP reverse triblock copolymer, a polynucleotide, a cationic surfactant and an amorphous cryoprotectant or crystalline bulking agent. Thus, the '322 patent does not provide a motivation to lyophilize DNA in the presence of a copolymer and a cryoprotectant. Here, the modification to the primary reference, Evans, would require a change in process from freezing the solution for the purpose of preserving the vaccine to lyophilizing, drying, the composition for the purpose of preservation. The combination of references does not

establish a *prima facie* case of obviousness because freezing is an operationally different procedure than lyophilizing.

iii. There is no motivation or suggestion to combine Evans and the '322 patent

Applicants invention is directed to providing a lyophilized formulation that will provide a useful DNA: vaccine product when resuspended. One of skill in the art would not have had an expectation that a formulation could be lyophilized and then resuspended to provide a stable formulation having the required DNA: adjuvant particle size. There is nothing in the combination of references that would suggest to the ordinary artisan to combine the reverse tri block copolymer of the '322 patent with a polynucleotide. Either alone or in combination, the references do not provide a motivation to prepare the lyophilized composition comprising a polynucleotide with the reverse triblock copolymer of the '322 patent and an amorphous cryoprotectant or crystalline bulking agent as now claimed. Accordingly, Applicants respectfully assert that a *prima facie* case of obviousness has not been established. Applicants respectfully request that the rejection be reconsidered and withdrawn.

Claims 4, 6 and 7 (Method)

The Examiner has rejected claims 4, 6 and 7 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Evans in view of Hunter *et al.* (U.S. Pat. No. 5,811,088; hereinafter "the '088 patent"). Specifically, the Examiner asserts that Evans "render obvious methods of mixing polynucleotide with POE-POP copolymers and cationic surfactants." (OA at page 8.) "[T]he hydrophilic POE portion (C2H4O) is

between approximately 1% and 40% by weight." (OA at page 3.) While the '088 reference "teach preparation and solubilization of copolymers in ice-cold phosphate buffered saline. The cold solution was filter sterilized on 0.22um filters and stored at 4°C." (OA at page 8, internal citations omitted.) "[T]he hydrophile portion represented by (2H4O) constitutes approximately 1% and 5-% by weight of the compound." (OA at page 8.)

i. There is no motivation or suggestion to combine Evans and the '088 patent

The claimed methods are not obvious because a person of ordinary skill in the art would not have been motivated to combine Evans and the '088 patent to arrive at the claimed invention. Evans does not teach making a composition comprising a block copolymer, a polynucleotide, a cationic surfactant, and a cryoprotectant selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and mixtures thereof, or a crystalline bulking agent. Because Evans does not teach the end product, a composition, as presently claimed, Evans cannot teach a method of making this composition. The Examiner acknowledges that "Evans did not teach a cold filtration step." (OA at page 8.) There is no teaching, motivation or suggestion in Evans that would lead the ordinary artisan to combine the reference with the '088 patent in order to arrive at the cold filtration step. Even if such a motivation would exist, the combination of references does not render the presently claimed invention obvious because the '088 patent does not recite all the necessary claim elements. The '088 patent reference does not teach lyophilizing or freeze drying compositions comprising a block copolymer, polynucleotide, cationic surfactant and an amorphous cryoprotectant or a crystalline bulking agent. The '088 patent reference does

not teach a polynucleotide / copolymer composition, or cold filtering a polynucleotide / copolymer composition. Thus, the '088 patent reference does not provide a motivation to use cold filtration with the composition of Evans. Accordingly, Applicants respectfully assert that a *prima facie* case of obviousness has not been established. Applicants respectfully request that the rejection be reconsidered and withdrawn.

Claims 25 and 26 (Product)

The Examiner has rejected claims 25 and 26 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Evans in view of Hunter *et al.* (U.S. Pat. No. 5,811,088; hereinafter "the '088 patent"). The shortcoming of Evans and '088 as they apply to the presently pending claims have been discussed above.

i. There is no motivation or suggestion to combine Evans and the '088 patent

The composition of claims 25 and 26 are not obvious because a person of ordinary skill in the art would not have been motivated to combine Evans and the '088 patent to arrive at the recited composition. The combination of references does not teach an amorphous cryoprotectant selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and mixtures thereof, or a crystalline bulking agent. The '088 patent does not teach lyophilizing or freeze drying a compositions comprising a block copolymer, polynucleotide, cationic surfactant and an amorphous cryoprotectant or a crystalline bulking agent. Since the '088 patent does not teach freeze drying the composition it cannot not teach reconstituting such a composition as required by claim 26. Because the combination of references does not teach all the claimed elements, Applicants respectfully assert that a

prima facie case of obviousness has not been established. Applicants respectfully request that the rejection be reconsidered and withdrawn.

Claims 11-14 (Method)

The Examiner has rejected claims 11-14 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Evans in view of Munsunuri *et al.* (WO 99/21591; hereinafter "Munsunuri"). The Examiner asserts that Munsunuri "teach compositions soluble ionic complexes comprising a surfactant and a polynucleic acid sequence." (OA at page 10.) "Example 1 shows mixing of a compositions comprising the surfactant, the polynucleic acid sequence, a phosphate buffer, tonicity agents such as sucrose, mannitol, trehalose or any other non-ionic agent." (OA at page 11.) Applicants respectfully traverse this rejections. The shortcomings of Evans as it applies to the presently-amended claims have been discussed above.

i. There is no motivation or suggestion to combine Evans and Munsunuri

The method of claims 11-14 are not obvious because a person of ordinary skill in the art would not have been motivated to combine Evans and Munsunuri to arrive at the recited method that requires an amorphous cryoprotectant selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and mixtures thereof, or a crystalline bulking agent. Here, Munsunuri does not teach or suggest using a copolymer for delivering a DNA containing composition. Munsunuri also does not suggest lyophilizing a DNA containing composition. There is no motivation in the references to combine the composition of Evans with the composition of Munsunuri. Accordingly, Applicants respectfully assert

that a *prima facie* case of obviousness has not been established. Applicants respectfully request that the rejection be reconsidered and withdrawn.

Other Matters

Chen *et al.* (U.S. Pat. No. 6,251,599) the reference does not teach using a block copolymer with a nucleic acid preparation, thus the reference does not teach or suggest all the claimed elements of the presently pending claims.

Neither Emanuele *et al.* (U.S. Pat. No. 5,990,241) nor Patel *et al.* (U.S. Pat. No. 5,990,241) teach making a lyophilized composition comprising a polyoxyethylene (POE) and polyoxypropylene (POP) block copolymer; a polynucleotide; a cationic surfactant; and a compound selected from the group consisting of monosaccharides, disaccharides, oligosaccharides, sorbitol, hydrophilic polymers, proteins and mixtures therof.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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